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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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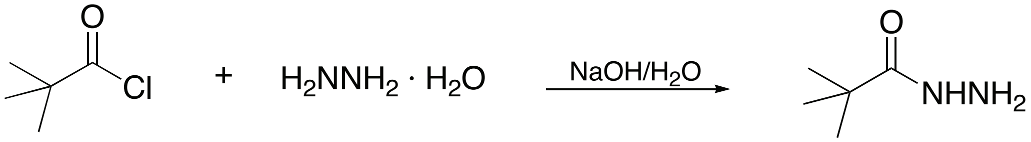
PREPARATION OF PIVALOYL HYDRAZIDE IN WATER
(Propanoic acid, 2,2-dimethyl-, hydrazide)



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Checked by Claire Coleman and Peter A. Wipf.

1. Procedure

Pivaloyl hydrazide. A 1-L, three-necked, round-bottomed flask equipped with a Teflon-coated thermocouple and mechanical stirrer is charged with 400 mL of water and sodium hydroxide (12.87 g, 322 mmol), and the resulting mixture is stirred until all of the solids dissolve (Note 1). Hydrazine (35% aqueous solution, 36.83 g, 400 mmol) is then added in one portion. The mixture is cooled in an ice-water/acetone bath to an internal temperature of –5 to 0 °C, and trimethylacetyl chloride (38.6 mL, 320 mmol) is added dropwise (Note 2) over a period of 40-60 min while maintaining the reaction temperature between –5 and 0 °C (Note 3). The reaction mixture is then transferred to a 1-L, pear-shaped flask and concentrated to a volume of ca. 100 mL by rotary evaporation (at ca. 100 mm) (Notes 4, 5) and the resulting suspension is filtered (Note 6). The filtrate is further concentrated to a volume of ca. 40 mL (Note 7) and 100 mL of toluene is then added. The resulting solution is transferred to a three-necked, round-bottomed flask equipped with a Dean-Stark water separator, thermometer, and rubber septum. Distillation is continued at atmospheric pressure until a constant boiling point is reached (Note 8) and then the pot volume is further reduced to ca. 40 mL. The resulting heterogenous mixture is filtered (Note 9) and the filtrate is concentrated by rotary evaporation under reduced pressure to provide the desired product as a colorless oil, which on standing solidifies to a white semi-solid. This material is recrystallized from 100 mL of isopropyl ether to afford 18.6-20.4 g (50-55%) of pivaloyl hydrazide (Notes 10, 11).

2. Notes

1. All reagents were purchased from Aldrich Chemical Company (except for trimethylacetyl chloride, which the checkers obtained from Acros) and were used without further purification. The checkers used a low temperature alcohol thermometer in place of a Teflon-coated themocouple. The third neck of the flask was left open to the atmosphere.

2. A syringe pump was used for the addition of acid chloride in order to achieve a steady flow rate. The tip of the syringe needle (gauge 20) was submerged in the reaction mixture. Dropwise addition of trimethylacetyl chloride at 0-5 °C resulted in the immediate formation of a precipitate.

3. The reaction was complete at the end of the pivaloyl chloride addition. On 5-L or larger scale, the reaction was conducted at temperatures of 10-15 °C without loss of selectivity.

4. A small amount of hydrazine hydrate was present in the reaction mixture at this point, but a safety evaluation indicated the final reaction mixture had a very low thermal potential (DH=15.3 J/g). This poses a minimum thermal hazard for vacuum distillation.

5. The submitters concentrated the reaction mixture by vacuum distillation (100 mm, bath temperature 70 °C, vapor temperature 51 °C). The weight after concentration was ca. 120 g. The checkers used rotary evaporation with a bath temperature of 65 to 70 °C without any problems, and employed an explosion shield as a safety precaution.

6. The bis-acylation byproduct ($Me_3CCONHNHCOCMe_3$) was removed by filtration; 20 mL of water was used for washing the filter cake.

7. The submitters removed solvent by vacuum distillation (100 mm, bath temperature 70 °C, vapor temperature 51 °C).

8. Azeotropic removal of water was complete when the vapor temperature reached 111 °C.

9. Sodium chloride was removed by filtration.

10. The submitters obtained the product in 72% yield without recrystallization and determined the product to be >97% pure by HPLC (by area; conditions: 250 mm Kromasil C4 column using acetonitrile (A)/water (B) and 0.1% TFA in water (C), 0:90:10 A:B:C ramp to 90:0:10 A:B:C over 15 min and hold for 5 min. Flow rate 1 mL/min and detection wavelength 210 nm. The checkers found the purity prior to recrystallization to be typically 85-90% with the impurity determined to be the bis-acylation product by LC-MS. The checkers employed C8 microsorb-MW 100 (250 mm) and Alltech C18 (100 mm) columns using acetonitrile (A)/water (B) and 0.1% TFA in water (C), 0:90:10 A:B:C ramp to 90:0:10 A:B:C over 15 min and hold for 5 min. Flow rate 1 mL/min and detection wavelength 210 nm.

11. The product exhibits the following physical properties: mp 67.1-69.2 °C; IR (NaCl) cm^{-1} 3471, 3327, 2968, 1660; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.19 (s, 9H), 4.40-4.85 (br, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 27.4, 38.1, 179.3; MS (*m/z*): 117 ([M + 1] $^+$). Anal. Calcd for $C_5H_{12}N_2O$: C, 51.70; H, 10.41; N, 24.12. Found C, 51.62; H, 10.78; N, 24.22.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practice in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Hydrazides ($RCONHNH_2$) are highly useful starting materials and intermediates in the synthesis of heterocyclic molecules.[2] They can be synthesized by hydrazinolysis of amides, esters and thioesters.[3] The reaction of hydrazine with acyl chlorides or anhydrides is also well known,[4] but it is complicated by the formation of 1,2-diacylhydrazines, and often requires the use of anhydrous hydrazine which presents a high thermal hazard. Diacylation products predominate when hydrazine reacts with low molecular weight aliphatic acyl chlorides, which makes the reaction impractical for preparatory purposes.[5]

Recently we needed to prepare large amounts of pivaloyl hydrazide (**1**). A literature survey indicated several approaches: (1) heating pivalic acid with hydrazine hydrate with a Lewis acid catalyst such as activated alumina[6] or titanium oxide;[7] (2) heating hydrazine hydrate at high temperature (140 °C) with ethyl pivalate;[8] (3) condensing phthaloyl hydrazine with pivaloyl chloride, followed by deprotection of the phthaloyl group;[9] and (4) reaction of ethyl thiopivalate with hydrazine hydrate. Reaction safety evaluations revealed that hydrazine monohydrate has an onset temperature of *ca.* 125 °C in a Differential Scanning Calorimetry (DSC) experiment, and possesses a very high thermal potential ($\Delta H = 2500$ J/g),[10,11] which prompted us to develop a method for the synthesis of **1** that did not require heating. After some experimentation we determined that the reaction of pivaloyl chloride with hydrazine proceeds most efficiently in water to give a 4:1 ratio[12] of **1** to $Me_3CCONHNHCOCMe_3$ (**2**). The use of organic solvents (MeOH, THF, 2-propanol) with water[13] invariably led to formation of biphasic mixtures and predominant formation of **2**.[14] Reaction workup is also simplified using water as solvent. Upon partial concentration the bis-acylhydrazide by-product **2** precipitated out of the reaction mixture and is conveniently removed by filtration. Removal of the remainder of the water by displacement with toluene leads to precipitation of NaCl, which is also easily removed by filtration. The filtrate is then further concentrated to provide **1** in >97% purity, typically in 55–75% yield. This procedure has been employed to prepare 10 Kg batches of **1** with no difficulty.

The protocol is effective in preparation of hydrazides of 5 carbons or less. Cyclopropanecarboxylic acid hydrazide[15] and isobutyric acid hydrazide[16] were prepared from their corresponding acid chlorides in 64% and 71% yields, respectively. However, when this method was applied to cyclohexanecarboxylic acid chloride, the bis-acylhydrazide was the predominant product, and the mono-acylhydrazide[17] was isolated in 25% yield.[18]

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10. Under nitrogen atmosphere, the thermal potential is slightly lower (DH = 2150 J/g), and the onset temperature is 150 °C.

11. For perspective, 1 g of hydrazine monohydrate is equivalent to ~0.5 g of 2,4,6-trinitrotoluene (TNT) in terms of thermal potential*;* T. Grewer, *Thermal Hazards of Chemical Reactions*; Elsevier:Amsterdam, **1994**, Vol. 4.

12. By integration of the ^{1}H NMR spectrum of the crude reaction product.

13. Water is still introduced from the use of hydrazine hydrate when no additional water is added.

14. Pivaloyl chloride and **1** are both preferentially soluble in the organic phase, which gives rise to **2** as the major product.

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18. Cyclohexanecarboxylic acid hydrazide has low solubility in water. A biphasic mixture developed during the reaction, which led to the predominant formation of the bis-acylated material.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Hydrazine; (10217-52-4)
Pivaloyl chloride: Propanoyl chloride, 2,2-dimethyl-; (3282-30-2)
Pivaloyl hydrazide: Propanoic acid, 2,2-dimethyl-, hydrazide; (42826-42-6)